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Effects of Clonidine Pretreatment on the Local Anaesthetic Activity of Bupivacaine in Mice

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Abstract

This study was designed to document possible changes in bupivacaine local anaesthetic activity in mice after a single injection of clonidine (0·1 or 1 mg kg^{-1}, i.p.). The local anaesthetic activity was evaluated during 60 min, according to a previously reported technique, using sciatic nerve blockade by injection of bupivacaine in the area of the sciatic nerve.

Clonidine pretreatment modified the local anaesthetic activity of bupivacaine dose-dependently. The time of recovery was higher for clonidine-pretreated mice (40·00 ± 7·24 min, 0·1 mg kg^{-1} clonidine: 50·0 ± 9·35 min, 1 mg kg^{-1} clonidine) compared with controls (27·22 ± 1·21 min, $P = 0·02$). The maximal effect (E_{max}) was significantly lower for the pretreated group (1·15 ± 0·13 units, 0·1 mg kg^{-1}; 1·35 ± 0·09 units, 1 mg kg^{-1}) compared with the control group (1·72 ± 0·13, $P = 0·01$).

Our data indicate a significant decrease in the duration of anaesthetic activity of bupivacaine in clonidine-pretreated mice.

Clonidine, an α_2-adrenoceptor agonist, has anaesthetic properties (Gaumann et al 1992) and its use in association with local anaesthetics (tetracaine, lignocaine) has been suggested in epidural anaesthesia (Carabine et al 1992). However there is little information on possible interactions between the two types of drug. In the light of our previous papers regarding drug interactions with the local anaesthetic bupivacaine (Bruguerolle 1993; Bruguerolle & Lorec 1994), the present work was initiated to document possible changes in local anaesthetic activity of bupivacaine in mice after a single injection of clonidine (0·1 and 1 mg kg^{-1}).

Materials and Methods

Adult male NMRI mice, 30 g, were housed five to a cage for a minimum of two weeks before use under controlled relative humidity (50–55%), temperature 24 ± 1°C and a light–dark cycle (lights on 0600–1800 h), during the month of March. The local anaesthetic activity was assessed using the previously reported method of Leszczynska & Kau (1992) which uses sciatic nerve blockade to determine local anaesthetic activity of drugs; the same technique may also determine the neuromuscular blocking effect. Briefly, before starting the experiment, the ability of each mouse to walk normally with four limbs on the top and on the inverted wire mesh screen (1 mm diam. wire, 5 mm mesh) was evaluated; only animals which met this criteria were retained for the experiment. Four groups of ten mice were used. Controls received a saline injection 30 min before bupivacaine treatment (group 1). Group 2 mice were treated with a single 0·1 mg kg^{-1} intraperitoneal dose of clonidine 30 min before bupivacaine injection. Group 3 mice were treated with a single 1 mg kg^{-1} intraperitoneal dose of clonidine 30 min before bupivacaine injection. Bupivacaine (8·25 mg kg^{-1} in a volume of about 0·05 mL) was injected (groups 1, 2 and 3) into the popliteal space of the posterior limb, in the area of the sciatic nerve. A fourth group (group 4) was injected with clonidine into the popliteal space (0·05 mg kg^{-1} in a volume of about 0·04 mL) to evaluate a possible specific local anaesthetic activity of clonidine. The local anaesthetic activity was evaluated as follows. Any animal that could not use the injected limb to walk normally on the top and on the inverted wire mesh screen was considered to have a positive response to local anaesthesia; local anaesthetic activity was rated as the loss of the motor control of the injected limb parameters (0 = normal use of the injected limb, 2 = impossibility of use of the injected limb). The evaluation was done at 1, 2, 3, 4, 5 min and every 5 min thereafter up to 60 min following bupivacaine injection. The score was plotted against time for each animal. For each group of ten mice, the maximal effect (E_{max}) was expressed by the highest score; the time of recovery was also evaluated for each animal. The total effect was estimated for each animal by using the area under the effect vs time curve (AUC_{0-60}) calculated by the trapezoidal rule. These parameters were all expressed as mean ± s.e.m. and compared by analysis of variance.

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Results

Fig. 1 shows the results of the evaluation of local anaesthetic activity during 60 min in the three groups; the time of recovery, the maximal effect (E_{max}) and the total effect (AUC_{0-60}) are summarized and compared in Table 1.

Clonidine pretreatment modified the local anaesthetic activity of bupivacaine dose-dependently. The time of recovery was higher for clonidine-pretreated mice (groups 2 and

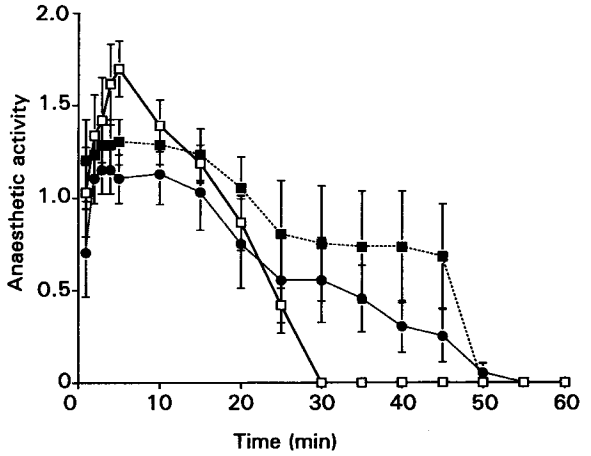

FIG 1. Bupivacaine local anaesthetic activity in □ controls (group 1 receiving bupivacaine 8·25 mg kg^{-1} alone) and clonidine-pretreated mice (● 0·1 mg kg^{-1} clonidine group 2, and ■ 1·0 mg kg^{-1} clonidine group 3). Values given are means ± s.e.m. (n = 10).

3) than for controls (40·00 ± 7·24, 50·00 ± 9·35 and 27·22 ± 1·21 min, respectively, $P = 0·02$). The maximal effect (E_{max}) was significantly lower for the pretreated group (groups 2 and 3) than for controls (1·15 ± 0·13, 1·35 ± 0·09 and 1·72 ± 0·13, respectively, $P = 0·01$) and the area under effect vs time curve was not statistically different ($P = 0·12$). In group 4, clonidine was found not to possess any local anaesthetic activity.

Discussion

The present work documents a significant decrease in the maximal local anaesthetic effect and a significant increase in the duration of activity of bupivacaine in clonidine-pretreated mice. Such an effect must be interpreted in the light of previously reported studies concerning concommitant use of clonidine and local anaesthetics since clonidine has been proposed to be combined with tetracaine or lignocaine for epidural anaesthesia (Carabine et al 1992). For example, clonidine intensifies and prolongs the analgesic effect of tetracaine (Bedder et al 1986; Mensik et al 1987; Bonnet et al 1989). More recently, Ota et al (1994) reported an effect of oral clonidine on prolonging sensory block during tetracaine spinal anaesthesia.

However, the possible interaction of the most commonly used anaesthetics, bupivacaine, with clonidine has not been studied in detail. Indeed, the few available studies deal mainly with the clonidine/bupivacaine interaction with respect to the possible modifications of bupivacaine toxicity; thus, De Kock et al (1993) recently reported that clonidine pretreatment reduces the systemic toxicity of intravenous bupivacaine in rats. De La Coussaye et al (1992) previously demonstrated that clonidine might improve ventricular electrophysiologic parameters in dogs, the antidysrhythmic properties of clonidine suggesting a possible protective effect of clonidine against bupivacaine cardiovascular toxicity. Further insight on the ability of clonidine to correct bupivacaine-induced ventricular electrophysiologic impairment was recently contributed by the same authors (De La Coussaye et al 1994), who hypothesized that the beneficial effect of clonidine on the variables of ventricular conduction altered by bupivacaine was mediated by the activation of the parasympathetic ganglionic nicotinic receptors.

Our present work, indicating a prolongation of action of bupivacaine in the presence of clonidine in mice, agrees with the previously reported data on other local anaesthetics such as tetracaine or lignocaine. This may be explained by pharmacokinetic modifications. The kinetics of bupivacaine after clonidine administration were recently reported in mice (Bruguerolle et al 1995); the maximal concentration of bupivacaine in serum as well as the area under its concentration curve were significantly higher in clonidine-pretreated mice while its clearance was decreased. Nevertheless, the volume of distribution of bupivacaine was not significantly modified. The ratio of AUC PPX/AUC bupivacaine (which may partially indicate the rate of metabolism) was lower in the presence of clonidine, suggesting a decreased hepatic metabolism in clonidine-treated mice.

In the present work, clonidine alone was found not to possess any proper local anaesthetic activity; this is in contradiction to the findings of Gaumann et al (1992, 1994) who demonstrated that clonidine displays local anaesthetic properties, albeit after direct application to a nerve fibre.

In conclusion, the salient result of the present work is a significant decrease in the maximal local anaesthetic effect and a significant increase in the duration of activity of bupivacaine in clonidine-pretreated mice; a pharmacokinetic drug interaction between clonidine and bupivacaine may account, at least partially, for these findings.

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Table 1. The effect of clonidine on the local anaesthetic activity of bupivacaine. Clonidine was injected 30 min before an injection of 8·25 mg kg^{-1} bupivacaine.

Clonidine (mg kg^{-1},i.p)	Recovery time (min)	E_{max} (units)	AUC_{0-60} (units h^{-1})
—	27·22 ± 1·21	1·72 ± 0·13	54·5 ± 7·2
0·1	40·0 ± 7·24*	1·15 ± 0·13**	51·1 ± 4·8
1·0	50·00 ± 9·35**	1·35 ± 0·09**	67·5 ± 5·4

Values are means ± s.e.m. (n = 10). *$P < 0·02$, **$P < 0·01$.

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